

AMENDMENTS TO THE SPECIFICATION:

Please amend the specification as shown:

Please delete the paragraph on page 6, line 31 to page 7, line 2 and replace it with the following paragraph:

Fig. 1 Sequence alignment of mouse Serca 1, 2 and 3 protein. Amino acid identity is designated by a dot. Gaps are designated by -. Amino acid substitutions in the Serca family proteins relative to mouse Serca1 protein are shown. Accession numbers for mouse Serca ATPases: mouse 1a, NP_031530; mouse 2a and 2b, NP_033852 and J131870; Serca3a, AAB04099; Serca3b, AAB04098; Serca3c, CAA75746 (SEQ ID NOS 14-19 are disclosed respectively in order of appearance).

Please delete the paragraph on page 7, lines 4-9 and replace it with the following paragraph:

Fig. 2 Sequence similarity of Serca2 proteins in mammalian species. Amino acid identity is designated by a dot. Gaps are designated by -. Amino acid substitutions in the Serca2 proteins in other species relative to mouse Serca2 are shown. Accession numbers for Serca2 ATPases: mouse 2a and 2b, NP_033852 and J131870; rat 2a, P11507; rat 2b, NP_058986; human 2a, NP_001672; human 2b, NP_733765; human 2c, AAO47398; dog 2a, O46674; cat 2a, Q00779; pig 2a and 2b, P11607; rabbit 2a and 2b, P20647 (SEQ ID NOS 20-32 are disclosed respectively in order of appearance).

Please delete the paragraph on page 7, lines 11-17 and replace it with the following paragraph:

Fig. 3 Targeting construct for Serca2 flox gene

modification. Sequence information. Partial DNA sequence information of the targeting vector is given. Gaps in the sequence are given by lines and text of positioning in the *atp2a2* gene. Introns are in italics. Coding sequence is in capital letters. Extra inserted material (cloning sites, antibiotics cassettes and loxP sites) is underlined. LoxP sites are in bold. Elements are placed into *atp2a2* gene intron 1, and intron 3 (2 positions). See figure 2 for schematic. The Serca2 gene sequence can be obtained from GenBank accession: NM_009722 (SEQ ID NOS 1-3 are disclosed respectively in order of appearance).

Please delete the paragraph on page 20, lines 12-28 and replace it with the following paragraph:

Construction of Serca2^{flox} mice: All genetic manipulations were performed using standard molecular biology techniques. The Serca2 (*atp2a2*) gene was cloned from a commercial genomic mouse lambda phage library (**129 SVJ from Stratagene**). A targeting vector, based on pBluescript II KS, containing 34 bp loxP sites (5'-ATA ACT TCG TAT AAT GTA TGC TAT ACG AAG TTA T-3'; SEQ ID NO: 4) placed into appropriate positions in *atp2a2* gene fragments and antibiotics selection genes was assembled

by standard cloning techniques. The targeting vector was named pSerca2T. All manipulations were confirmed by DNA sequencing (see figure 3). The targeting vector was introduced into mouse embryonic stem cells (ES cells) by standard techniques (electroporation). ES cells carrying homologous recombination events with correctly placed loxP sequences were enriched by antibiotics selection procedures, and identified by Southern hybridization techniques and PCR. The antibiotics selection genes were then excised by a second round of electroporation with a Cre recombinase-expressing plasmid. Correct clones were again identified by Southern blotting and PCR. The final result of the genetic manipulations was that two loxP sites and additional necessary cloning and restriction sites were introduced into 2 separate introns in the *atp2a2* gene. The modification is outlined in figure 4.

Please delete the paragraph on page 21, lines 16-29 and replace it with the following paragraph:

PCR detection: Different alleles of the Serca2 gene (Serca2 wt, flox or deletion) and the MLC-2v gene (wt and cre knock-in) were detected by standard PCR reactions with annealing temperature of 55 °C for 25-30 cycles and Amplitaq Gold on an ABI 9600 thermocycler (Applied Biosystems).

Primers were as follows:

OL84 5'- cca agg aag atg gct gac c - 3' (SEQ ID NO: 5)

OL85 5'- cat cga cgc ctc ata aat cc - 3' (SEQ ID NO: 6)

OL86 5'- tct tca taa cac acg cca att t - 3' (SEQ ID
NO: 7)

OL87 5'- ccc ttt gct gcc aat taa cta tt - 3' (SEQ ID
NO: 8)

OL88 5'- acc tct agg ggt ctc gaa tca - 3' (SEQ ID NO: 9)

OL102 5'- aag ttg aat aac cgg aaa tgg ttt - 3' (SEQ ID NO:
10)

OL103 5'- tgt tat aag caa tcc cca gaa atg - 3' (SEQ ID NO:
11)

OL104 5'- agg ctc ctc gaa ctc tcc ag - 3' (SEQ ID NO:
12)

OL105 5'- gta aga gag ctt ccc tcc tcc tt - 3' (SEQ ID
NO: 13)